

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A01N 43/46	A1	(11) International Publication Number: WO 00/30446 (43) International Publication Date: 2 June 2000 (02.06.00)
<p>(21) International Application Number: PCT/US99/27481</p> <p>(22) International Filing Date: 19 November 1999 (19.11.99)</p> <p>(30) Priority Data: 60/109,611 23 November 1998 (23.11.98) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/109,611 (CON) Filed on 23 November 1998 (23.11.98)</p> <p>(71)(72) Applicant and Inventor: DAVIS, Bonnie [US/US]; 160 Cold Spring Road, Syosset, NY 11791 (US).</p> <p>(74) Agents: RICHARDS, John; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS</p> <p>(57) Abstract</p> <p>Acetylcholinesterase inhibitors are of use for treating a variety of diseases and conditions including Alzheimer's disease. They also affect circadian rhythms. In order to optimize the use of such compounds, the present invention provides dosage forms and methods of treatment wherein an effective amount of a centrally-acting acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined period. Suitable acetylcholinesterase inhibitors include galanthamine, lycoramine, analogs thereof and rivastigmine.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Dosage Formulations for Acetylcholinesterase Inhibitors

Field of the Invention

The present invention relates to dosage forms for cholinesterase inhibitors that will assist in obviating some of the undesirable side effects of use of such drugs and in methods of administering such drugs for this purpose.

Background of the Invention

Recently there has been considerable interest in the use of several drugs in this class including tacrine, donepezil, physostigmine, rivastigmine and galanthamine for the treatment of Alzheimer's disease. Cholinergic drugs are known to have an effect on the body's circadian rhythms and in U. S. Patent 5585375, I have claimed the use of galanthamine for treatment of jet lag. Although beneficial in some respects, circadian effects of cholinergic drugs may cause problems for care givers in cases where the patient is unable to take care of his or herself since it can result in the patient becoming active and needing attention during the night.

Summary of the Invention

The object of the present invention is to time the release of acetylcholinesterase-inhibiting medication so as to provide it on a suitable physiological schedule, for example to ensure that it can be taken while a patient is awake in the evening and will be acting at the time of expected awakening in the morning and to provide dosage forms suitable for this purpose.

From a first aspect, the present invention provides dosage forms of a pharmaceutical composition which comprise an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period. For example in one aspect such delay will be for a period of four to twelve hours so

that a dose may be administered to the patient in the evening and allow a night's sleep before the acetyl cholinesterase inhibitor becomes active in the morning. The duration of delay chosen will depend upon the exact way in which it is chosen to administer the drug. For example if it is intended to administer the drug with an evening meal taken at, say 6:30 in the evening a twelve hour delay may be appropriate if one wishes the drug to be active the following morning. If the desired time of administration is bed time, however, a six or seven hour delay may be more useful.

From a second aspect, the present invention provides a method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally acting acetylcholinesterase inhibitor, such as Alzheimer's disease, which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period prior to acetylcholinesterase inhibition being desired.

Detailed Description of the Invention

Acetylcholinesterase inhibitors of use in the present invention are those that have a central effect and have a medium duration of action (typically from 2 to 12 hours) for the treatment of diseases where acetylcholinesterase inhibiting activity in the brain is desired, especially in the treatment of Alzheimer's disease. Suitable acetylcholinesterase inhibitors will typically have a half life in the body of from 1 to 11 hours and once released from the dosage form will pass easily through the blood-brain barrier. The most suitable compounds for this purpose are galanthamine, lycoramine and their analogs wherein wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an

alkanoyloxy group, a benzyloxy or substituted benzyloxy group, a carbonate group or a carbamate group;

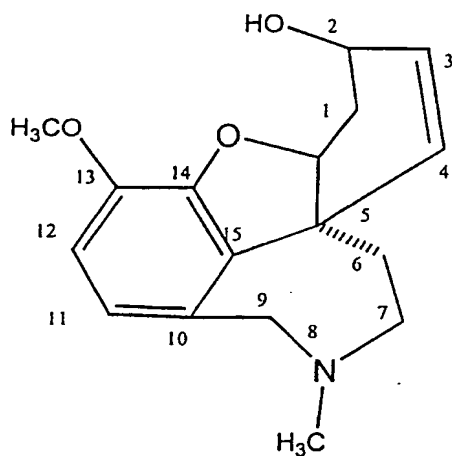
the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl group or a substituted or unsubstituted benzyloxy group.

When reference is made to a substituent group, said group may be selected from alkyl or alkoxy groups of from 1 to 6 carbon atoms, halo groups, and haloalkyl groups such as trifluoromethyl.

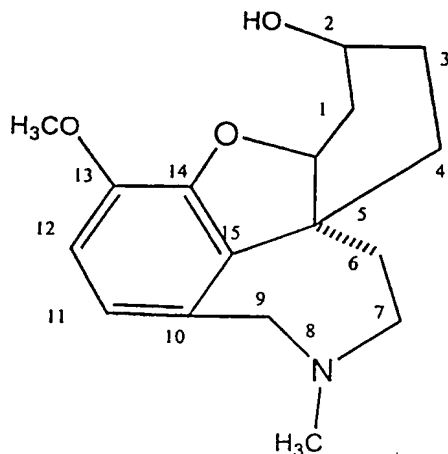
One or more of the methoxy, hydroxy and methyl groups of galanthamine or lycoramine may be replaced by the groups noted above.

Galanthamine and lycoramine have the following formulae:

Galanthamine



Lycoramine



Suitable analogs are described for example in International Patent Publication WO88/08708 and an article by Bores and Kosley in *Drugs of the Future* 21: 621-631 (1996). Other useful pharmacologic agents for such preparations include rivastigmine, and other pharmacologic agents with half lives of 1-11 hours.

Particularly useful analogs of galanthamine and lycoramine that are of use in the present invention include analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group, for example an alkanoyloxy or benzoyl group, of from one to seven carbon atoms or where methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from

alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Other useful analogs include compounds wherein, independently of whether or not the methoxy group has been replaced, the hydroxy group is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an acyloxy group, for example an alkanoyloxy group, typically of from 1 to 7 carbon atoms, a benzoyloxy or substituted benzoyloxy group wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups, a carbonate group or a carbamate group which may be a mono or dialkyl or an aryl carbamate or carbonate wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Although a major use of the present invention will be in the treatment of Alzheimer's disease, it is also suitable for treatment of other diseases or conditions in which there is need for increased brain acetyl choline levels after a defined period. Thus it may find use, for example for healthy persons who have need for increased acetyl choline levels some specified time in the future, for example workers changing from a day shift to a night shift or vice-versa.

In Alzheimer's disease, the primary and universal neurochemical abnormality is a deficit of acetylcholine. The normal pattern of brain acetylcholine is elevated release just before and during the time of activity, and reduced release during sleep. (Kametani, 1991; Mizuno, 1991) The brain content of acetylcholine exhibits a reciprocal relationship with release patterns, presumably representing stored neurotransmitter. (Saito, 1974) Likewise, acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks during the subjective night, and is lowest during activity periods. (Schiebeler, 1974) Consistent with these experimental results is the long-recognized diurnal variation of human bronchial constriction from acetylcholine inhalation, being most sensitive in the evening,

when endogenous cholinergic activity would be expected to be low, and least sensitive during waking hours, when cholinergic systems would be expected to be active (Reinberg, 1974) Humans are also sensitive to the systemic administration of the acetylcholinesterase inhibitors, physostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low. These disturb sleep and produce awakenings. (Sitaram, 1979, Reimann, 1994)

Animals who are made hypocholinergic either by disruption of the high affinity choline uptake system or by being raised on a false cholinergic neurotransmitter have a reduced circadian variation of acetylcholine and a disrupted diurnal rhythm of locomotor activity, which correlates with the cholinergic hypoactivity. (Morley 1989, Szymusiak, 1993) This same situation exists in Alzheimer patients who have both cholinergic deficits and disruption of normal sleep-wake cycles. It is of major practical importance because a patient who requires twenty-four hour supervision wears out a single caretaker, requiring multiple shifts of caretakers, or institutionalization, which is expensive, frightening to the patient, and sad for the family. (see New York Times article, July 27, 1998) An additional potential utility of a dosage form which can be taken when convenient, and active when needed, would therefore be the superimposition of a physiological rhythm of cholinergic activity, via a pill, onto a brain in which the cholinergic system is deteriorating.

Preparations for treatment of Alzheimer's disease, containing cholinomimetic agents, may stimulate intestinal peristalsis as they are released, thus promoting their own passage through the gastrointestinal tract. It may therefore be useful to incorporate into the dosage unit, or to manufacture a second, similarly timed tablet, to deliver an anticholinergic agent designed to remain outside the blood brain barrier, in order to reduce gastrointestinal motility. The anticholinergic tablet might contain, for example, probanthine, 7.5-60 mg, or robinul 1 to 8 mg. A desirable formulation for an Alzheimer patient for whom sleeping hours of 11 pm to 7 am are desirable might be a pill which could be taken at bedtime and begin to release galanthamine at 5 am at a rate of 3 mg (measured as base) per hour for 4 hours, or 2 mg/hour for 6 hours beginning at 4 am. The same pill, taken at 7 am, would cover the daytime hours.

This should allow the central nervous system to become relatively hypocholinergic at the time of desired sleep, as the half life of galanthamine has been reported to be 4.5-8 hours. (Thomsen, 1990)

Alternatively, a single pill may deliver a full day's medication, although there is some risk of dumping an excessive dose, which could be dangerous in the case of cholinergic medications. The delay before release of active medication could be chosen between one and 11 hours depending on whether the pill is to be taken at dinner or bedtime.

Likely pharmacologic agents for such preparations include galanthamine, rivastigmine, and other pharmacologic agents with half lives of 1-11 hours. Dosage units for twice daily administration should contain from 4-16 mg of galanthamine (as base), or 2-10 mg of rivastigmine, both of which should be doubled in the case of once per day dosage units. Dosages for other suitable agents can be determined by standard techniques such as those set out for example in Chapter 6 (by Benjamin Calesnick) of Drill's Pharmacology in Medicine (Fourth Edition Joseph R DiPalma ed, McGraw-Hill 1971 or in Chapter 6 (by B. E. Rodda et al) of Biopharmaceutical Statistics for Drug Development (ed. Karl E. Peace, Marcel Dekker Inc, 1988). Anticholinergic agents, if needed, could be probanthine, 7.5-60 mg, to be delivered at the same time as the cholinomimetic agents, or robinul (1 to 8 mg) or similar agents incorporated so that a typical dose is delivered within the time frame of the cholinomimetic release.

Delayed action formulations for use in the present invention typically are those used for oral administration and include tablets, capsules, caplets and other convenient devices. Such dosage units may be prepared by methods well known to those skilled in the art, such as those described in Sustained Release Medications by J.C. Johnson, Noyes Data Corporation, 1980, and an article by Conte et al in Biomaterials 1993 vol 14 pages 1017 to 1023 entitled Press-coated tablets for time-programmed release of drugs, both of which are incorporated herein by reference. For example the active compounds may be coated or incorporated in a matrix which controls the elapse of between administration of the dose and the time at which release is desired.

What I claim is:

1. A dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined period.
2. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from four to twelve hours.
3. A dosage form of a pharmaceutical composition as claimed in claim 2 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from six to nine hours.
4. A dosage form of a pharmaceutical composition as claimed in claim 2 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from eight to twelve hours.
5. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor has a duration of action of from 2 to 12 hours.
6. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor has a half life of from one to eleven hours
7. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein the methoxy group thereof is replaced by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

8. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.
9. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the N-methyl group of galanthamine or lycoramine is replaced by hydrogen, alkyl, benzyl or a cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.
10. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.
11. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms
12. A dosage form as claimed in claim 11 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms
13. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group

wherein the alkyl groups contain from 1 to 8 carbon atoms.

14. A dosage form as claimed in claim 12 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms
- 15 A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.
- 16 A dosage form as claimed in claim 8 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.
- 17 A dosage form as claimed in claim 8 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.
- 18 A dosage form of a pharmaceutical composition as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

19. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is galanthamine.
20. A dosage form as claimed in claim 1 wherein said acetylcholinesterase inhibitor is rivastigmine.
21. A method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally acting acetylcholinesterase inhibitor which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period prior to acetylcholinesterase inhibition being desired.
22. A method of treatment as claimed in claim 21 wherein said patient is suffering from Alzheimer's disease.
23. A method of treatment as claimed in claim 21 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from four to twelve hours.
24. A method of treatment as claimed in claim 23 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from six to nine hours.
25. A method of treatment as claimed in claim 23 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from eight to twelve hours.
26. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor has a duration of action of from 2 to 12 hours.

27. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor has a half life of from one to eleven hours

28 A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl or a substituted or unsubstituted benzoyloxy group.

29. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

30 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

31. A method of treatment as claimed in claim 30 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

32. A method of treatment as claimed in claim 31 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.
33. A method of treatment as claimed in claim 32 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms
34. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.
35. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.
36. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.
37. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is galanthamine.

38. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is rivastigmine.
39. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is administered in conjunction with a compound that reduces its peripheral effects.
40. A method of treatment as claimed in claim 39 wherein said acetylcholinesterase inhibitor is administered in conjunction with a suitable dose of probanthine or robinul.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27481

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A01N 43/46

US CL :514/215, 214

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/215, 214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,900,748 A (BROSSI et al.) 13 February 1990, see abstract and columns 1 and 2.	1-40
Y	US 5,668,117 A (SHAPIRO) 16 September 1997, see abstract and claims 1 and 4.	1-40
Y	CONTE, U. et al. Press-coated tablets for time-programmed release of drugs. Biomaterials. 1993, Vol. 14, No. 13, pages 1017-1023, entire document.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

13 MARCH 2000

Date of mailing of the international search report

06 APR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

DWAYNE C. JONES

Telephone No. (703) 308-1235

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27481

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, CA, BIOSIS, USPATFULL, MEDLINE, DRUGU, TOXLINE, TOXLIT search terms include: lycoramine, galanthamine, delayed##(3a)releasc###, neurodegenerative(3a)disease#, alzheimer?